

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 1528-351-1PC	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 99/ 20541	International filing date (day/month/year) 07/09/1999	(Earliest) Priority Date (day/month/year) 08/09/1998
Applicant THE GOVERNMENT OF THE UNITED STATES...et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

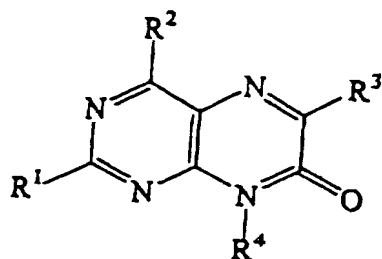
☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The invention provides pteridine nucleotides of formula (I) which are highly fluorescent and which can be used in the chemical synthesis of fluorescent oligonucleotide. The invention further provides for fluorescent oligonucleotide comprising one or more pteridine nucleotides. In addition the invention provides for pteridine nucleotide triphosphates which may be used as the constituent monomers in DNA amplification procedures. The pteridine nucleotides are more stable and possess higher quantum yields than structurally similar pteridine nucleotides.



(I)

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07H19/06 C07H21/00 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JUNGMAN O ET AL: "Pteridine nucleoside analogs of 2'-deoxyadenosine as building blocks for oligonucleotide synthesis" NUCLEOSIDES NUCLEOTIDES (NUNUD5,07328311);1997; VOL.16 (5 & 6); PP.863-868, XP002122656 Univ. Konstanz;Fakultat Chemie; Konstanz; D-78434; Germany (DE)	1-45
X	the whole document, but especially page 865, scheme, compounds 10,14-16,20-22,26-28,32,33 --- -/--	1-8, 10-21,29

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

15 November 1999

Date of mailing of the international search report

03/12/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Scott, J

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HAWKINS M E ET AL: "Fluorescence properties of pteridine nucleoside analogs as monomers and incorporated into oligonucleotides" ANAL. BIOCHEM. (ANBCA2,00032697);1997; VOL.244 (1); PP.86-95, XP002122657 NIH;National Cancer Inst.; Bethesda; 20892-1928; MD; USA (US)	1-45
X	the whole document, but especially compound 25 on page 87	1,2,18,29
Y	WO 98 26093 A (US HEALTH ;HAWKINS MARY (US)) 18 June 1998 (1998-06-18) the whole document	1-45
Y	WO 95 31469 A (US HEALTH) 23 November 1995 (1995-11-23) the whole document & US 5 525 711 A cited in the application	1-45
X	TAYLOR E C ET AL: "Condensation of phosphonate anions with 4-amino-5-nitrosopyrimidines: new pteridine synthesis" J. CHEM. SOC. D. (CCJDAO);1971; (4); PP.189, XP002122658 Princeton Univ.;Dep. Chem.; Princeton; N. J. page 189, table, (I) R = Me (H for Ph at C-2)	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/20541

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9826093	A	18-06-1998	AU	7847798 A	03-07-1998
WO 9531469	A	23-11-1995	US	5525711 A	11-06-1996
			AT	167680 T	15-07-1998
			AU	688036 B	05-03-1998
			AU	2399195 A	05-12-1995
			CA	2190588 A	23-11-1995
			DE	69503129 D	30-07-1998
			DE	69503129 T	18-02-1999
			EP	0759927 A	05-03-1997
			ES	2118593 T	16-09-1998
			JP	10500949 T	27-01-1998
			US	5612468 A	18-03-1997

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1528-351-1PC	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) FOR FURTHER ACTION	
International application No. PCT/US99/20541	International filing date (day/month/year) 07/09/1999	Priority date (day/month/year) 08/09/1998
International Patent Classification (IPC) or national classification and IPC C07H19/06		
Applicant THE GOVERNMENT OF THE UNITED STATES...et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 13/03/2000	Date of completion of this report 02.11.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Korsner, S-E Telephone No. +49 89 2399 8554 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/20541

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-43 as originally filed

Claims, No.:

1-45 as originally filed

Drawings, sheets:

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 17.1);
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/20541

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	(9, 22-28, 30-45)
	No:	Claims	(1-8, 10-21, 29)
Inventive step (IS)	Yes:	Claims	to be settled
	No:	Claims	idem
Industrial applicability (IA)	Yes:	Claims	1-45
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

V. Reasoned statement

The following documents will be referred to in this report:

D1 = Nucleosides & Nucleotides; 1997, pages 863-868

D2 = J. Chem. Soc. D; 1971, page 189

D3 = Anal. Biochem; 1997, pages 86-95

D4 = WO - A - 9826093

1. Novelty (Article 33(2) PCT)

1.

It is obvious from the cited prior art, especially D1, that the proposed concept is already known.

The disclosure of D1 is pertinent to a number of claims (including preferred compounds), as already indicated in the search report.

2.

A novelty-destroying compound is found also in D2.

3.

Although the specific compounds of D1 are monomers, it is clear from the title that they are intended as building blocks for oligonucleotide synthesis. The novelty-destroying effect can therefore be seen as more extensive than indicated in the search report.

The statement in Box V has therefore been put in parentheses.

2. Inventive step (Article 33(3) PCT)

Even if novelty can be restored, the inventive step must be based on a further contribution to the art that would not have been achieved by the skilled man by routine optimisation of the teachings of D1 in combination with, for instance, the relevant parts of D3 (see the sequences) and D4 (see the hairpin formation).

The Description does not stress a particular feature that immediately could be seen as a basis for an inventive step.

It rather suggests the use of the known property (strong fluorescence) on a general scale with a large number of compounds, some of which being already known. Note also the statements on pages 7-8 of the Description which suggest that the protective groups (see R2, R7) are well-known to the skilled man.

Whereas most method claims, and the kit, are stated to be novel, there seems to be no inventive step involved in these claims.

No further information has been submitted by the Applicant during the international phase.

The question of inventive step should therefore be settled in a later phase.

The Applicant's attention is drawn to the fact that restrictions, which result in structurally different subgroups, could give rise to a non-unity objection.

All claims should have one and the same inventive feature in common.

VIII. Certain observations

Claims:

1.

Claim 1 contains several inconsistencies

- a nitrogen atom is tetravalent (see the first formula)
- a carbon atom is pentavalent (-----idem-----)
- the proviso on line 22 is irrelevant since R1 cannot be L

The incorrect proviso is also present in Claims 18 and 29.

2.

The reference to oligonucleotides in Claim 18 is unclear in so far as these oligonucleotides may comprise one monomer only.

3.

The sequences of Claim 28 should preferably be present as such in the claim; note that most of the sequences appear twice in Table 2 and the actual number of sequences would therefore be 12 only.

4.

Claim 29 could be simplified by the use of claim dependency when defining the compound.

Description:

5.

The first statement on page 1 may only be necessary in a later US phase?

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/20541

6.

Statements such as "incorporated herein by reference" (pages 1-2 and 43) are not acceptable under certain national/regional regulations (e.g. in a later European phase).

7.

The figure on page 2 is incorrect; see remark 1 above.

8.

The "including, but not limited to" should be deleted in the definitions on pages 2-3, because the Description shall correspond to the claims.

9.

The proviso about R1/R4 should be deleted on page 3.

10.

The terms "Teflon" (i.a. page 15) and "Ludox" (page 36) appear to be registered trade marks and should then be identified as such; the applicant should be to include a list of these trade marks, e.g. on page 43.

11.

The statements on page 43, lines 11-16, have no clear interpretation.

Prior art (Rule 5.1(a)(ii) PCT)

The documents D1-D4 should be identified in the Description and their background art be briefly discussed.

Finally,

The Description has to be amended and restricted in view of the cited prior art.

- - - - -

PATENT COOPERATION TREATY

TOWNSEND & TOWNSEND
& CREW
From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:
TOWNSEND AND TOWNSEND AND CREW
Attn. SNYDER, J.
Two Embarcadero Center, 8th Floor
San Francisco, CA 94111-3834
UNITED STATES OF AMERICA

Date of mailing
(day/month/year) 03/12/1999

Applicant's or agent's file reference
1528-351-1PC

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US 99/ 20541

International filing date
(day/month/year) 07/09/1999

Applicant

THE GOVERNMENT OF THE UNITED STATES...et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.


4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority

 European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

John De Bruijn

DOCKETED
2-3-00

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

00 NOV 10 AM 10:24

PCT

CHAMBERS, Guy W. et al
TOWNSEND AND TOWNSEND AND CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, CA 94111-3834
ETATS-UNIS D'AMERIQUE

RECEIVED

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing

(day/month/year)

02.11.2000

Applicant's or agent's file reference

1528-351-1PC

IMPORTANT NOTIFICATION

International application No.

PCT/US99/20541 ✓

International filing date (day/month/year)

07/09/1999 ✓

Priority date (day/month/year)

08/09/1998 ✓

Applicant

THE GOVERNMENT OF THE UNITED STATES...et al. ✓

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

318/01

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Gallego, A

Tel. +49 89 2399-8102





Km

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1528-351-1PC		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/20541	International filing date (day/month/year) 07/09/1999	Priority date (day/month/year) 08/09/1998	
International Patent Classification (IPC) or national classification and IPC C07H19/06			
Applicant THE GOVERNMENT OF THE UNITED STATES...et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 			
Date of submission of the demand 13/03/2000		Date of completion of this report 02.11.2000	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Korsner, S-E Telephone No. +49 89 2399 8554 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/20541

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*

Description, pages:

1-43 as originally filed

Claims, No.:

1-45 as originally filed

Drawings, sheets:

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 28.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/20541

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	(9, 22-28, 30-45)
	No:	Claims	(1-8, 10-21, 29)
Inventive step (IS)	Yes:	Claims	to be settled
	No:	Claims	idem
Industrial applicability (IA)	Yes:	Claims	1-45
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

V. Reasoned statement

The following documents will be referred to in this report:

D1 = Nucleosides & Nucleotides; 1997, pages 863-868

D2 = J. Chem. Soc. D; 1971, page 189

D3 = Anal. Biochem; 1997, pages 86-95

D4 = WO - A - 9826093

1. Novelty (Article 33(2) PCT)

1.

It is obvious from the cited prior art, especially D1, that the proposed concept is already known.

The disclosure of D1 is pertinent to a number of claims (including preferred compounds), as already indicated in the search report.

2.

A novelty-destroying compound is found also in D2.

3.

Although the specific compounds of D1 are monomers, it is clear from the title that they are intended as building blocks for oligonucleotide synthesis. The novelty-destroying effect can therefore be seen as more extensive than indicated in the search report.

The statement in Box V has therefore been put in parentheses.

2. Inventive step (Article 33(3) PCT)

Even if novelty can be restored, the inventive step must be based on a further contribution to the art that would not have been achieved by the skilled man by routine optimisation of the teachings of D1 in combination with, for instance, the relevant parts of D3 (see the sequences) and D4 (see the hairpin formation).

The Description does not stress a particular feature that immediately could be seen as a basis for an inventive step.

It rather suggests the use of the known property (strong fluorescence) on a general scale with a large number of compounds, some of which being already known. Note also the statements on pages 7-8 of the Description which suggest that the protective groups (see R2, R7) are well-known to the skilled man.

Whereas most method claims, and the kit, are stated to be novel, there seems to be no inventive step involved in these claims.

No further information has been submitted by the Applicant during the international phase.

The question of inventive step should therefore be settled in a later phase.

The Applicant's attention is drawn to the fact that restrictions, which result in structurally different subgroups, could give rise to a non-unity objection.

All claims should have one and the same inventive feature in common.

Viii. Certain observations

Claims:

1.

Claim 1 contains several inconsistencies

- a nitrogen atom is tetravalent (see the first formula)
- a carbon atom is pentavalent (-----idem-----)
- the proviso on line 22 is irrelevant since R1 cannot be L

The incorrect proviso is also present in Claims 18 and 29.

2.

The reference to oligonucleotides in Claim 18 is unclear in so far as these oligonucleotides may comprise one monomer only.

3.

The sequences of Claim 28 should preferably be present as such in the claim; note that most of the sequences appear twice in Table 2 and the actual number of sequences would therefore be 12 only.

4.

Claim 29 could be simplified by the use of claim dependency when defining the compound.

Description:

5.

The first statement on page 1 may only be necessary in a later US phase?

6.

Statements such as "incorporated herein by reference" (pages 1-2 and 43) are not acceptable under certain national/regional regulations (e.g. in a later European phase).

7.

The figure on page 2 is incorrect; see remark 1 above.

8.

The "including, but not limited to" should be deleted in the definitions on pages 2-3, because the Description shall correspond to the claims.

9.

The proviso about R1/R4 should be deleted on page 3.

10.

The terms "Teflon" (i.a. page 15) and "Ludox" (page 36) appear to be registered trade marks and should then be identified as such; the simplest remedy would be to include a list of these trade marks, e.g. on page 43.

11.

The statements on page 43, lines 11-16, have no clear interpretation.

Prior art (Rule 5.1(a)(ii) PCT)

The documents D1-D4 should be identified in the Description and their background art be briefly discussed.

Finally,

The Description has to be amended and restricted in view of the cited prior art.
